REMARKS

Claims 1, 3-13, 15-25, 27-41 and 43-56 are currently pending in the application and are addressed herein.

Claim Rejections - 35 USC § 112

The Examiner has rejected claims 1,3-13, 15-25, 27-41, 43-56 under 35 U.S.C. 112, first paragraph. The Examiner contends that the specification is enabled for methods comprising administering, directly to a cell, a mRNA sequence or a DNA sequence encoding said mRNA sequence. However, the Examiner contends that the claims are not enabled for any route of administration other than administration directly to the target cells.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman.* They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Applicants respectfully disagree with Examiner and contend that the Examiner is mistaken on the state of the art and that present specification fully meets the requirements set out above as further explained below.

Applicants respectfully ask Examiner to consider the following guidance:

The nature of the invention

The instant claims are drawn to methods which encompass administering a either a mRNA sequence or a DNA encoding the mRNA, wherein the mRNA sequence comprising a translatable sequence encoding a toxin and an untranslatable sequence that inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eIF4E but which allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eIF4E relative to normal cells.

The breadth of the claims

The Examiner contends that with respect to the mode of administration, the claims are very broad since the claims do not particularly indicate any specific type route of administration, the claims encompass any route of administration, including systemic administration of the therapeutic nucleic acid. Applicants respectfully point out that the route of administration is not pertinent to the present invention and, in any case, are no broader than inherent in the average therapeutic composition. Administration is dictated by the nature of the invention and is easily ascertained by one skilled in the art.

The unpredictability of the art and the state of the prior art.

The Examiner contends that the administration of the therapeutic nucleic acid to a part of the body other than site of the target cells (in this case, the tumor cells), it is well established in the art that delivery is one of the key problems of gene therapy. The Examiner cites Anderson (Nature 1998; 392(suppl):25-30) as stating "[t]he challenge is to develop gene therapy as an efficient and safe drug delivery system."

Applicants respectfully point out that the very crux of the present invention is that it frees the practitioner from the "challenge of an efficient and safe drug delivery system." The present invention provides for a therapeutic that can be delivery to any and all cells of the subject since they are only activated within the target cells. Delivery to other cells is immaterial.

The Examiner continues in citing Crystal (Science 1995; 270:404-410) as indicating some of the problems regarding gene therapy in general stating "the [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." Applicants respectfully point out that the present specification clearly proves that the therapeutic can, in fact, be delivered to its target and that it can be delivered without recognition by the immune system.

As described below, the experiments carried out by DeFatta and De Benedetti (*Cancer GeneTherapy* 9:502-512 – 2002) and which were included in the Patent Application as examples, were carried out with immunocompetent animals (BalbC mice). Therefore, the Examiner's assertion is without scientific basis.

Regarding the efficacy of GDEPT therapy, The Examiner cites Kirn et al. stating "Several advantages [of GDEPT] can be defined: enhanced selectivity of toward cancer cells, amplification effects, and bystander cell death. However, technical hurdles related to the delivery of the foreign gene by viral or non-viral vectors remain to be overcome before reaching therapeutic success. Thus the main requirement for the future is efficient targeting and delivery."

Again, Applicants respectfully point out that the present specification clearly proves that the therapeutic can, in fact, be delivered to its target and that it can be delivered without recognition by the immune system and act as a successful therapeutic. (See attached Declaration of A. DeBenedetti). Furthermore, the data provided is far greater than what is often available in many issued patents.

Working Examples and Guidance in the Specification

The Examiner has misstated the showing of the working examples and guidance in the specification in stating that"

> "[T]he working examples only show systemic administration of a DNA to an immunocompromised mouse. There are no working examples show systemic administration of a DNA to a mouse that has a fully functional immune system. Therefore, there are no working examples showing that the claimed invention overcomes the unpredictability recognized in the art.

In the present application, the inventors have demonstrated efficacy in immunocompetent (BalbC mice) in addition to the immunocompromised mice (see DeFatta RJ, Chervenak RP, De Benedetti A. A cancer gene therapy approach through translational control of a suicide gene. Cancer Gene Ther. 2002, Jun; 9(6):505-12.; and 5) immune status does not appear to play a role in determining efficacy of translational control for HSV-TK gene therapy (See, for example, Chu QD, Sun L, Li J, Byrnes K, Chervenak D, Debenedetti A, Mathis JM, Li BD. A rat adenocarcinoma cell line infected with an adenovirus carrying a novel herpes-simplex virus-thymidine kinase suicide gene construct dies by apoptosis upon treatment with ganciclovir. J Surg Res. 2007

Nov;143(l):189-94; Byrnes K, Li BD, Holm N, Li J, Okadata Y, De Benedetti A, Nedeljkovic-Kurepa A, Mathis M, Chu QD. A novel suicide gene therapy targeting the overexpression of eukaryotic initiation factor 4E improves survival in a rat peritoneal carcinomatosis model. Surgery. 2007 Aug;142(2):270-5.).

The Examiner is taking generalized statements about gene therapy to state that the present invention *might not work* despite a showing in the specification that the present invention does, in fact, work.

Contrary to the Examiner's assertions, Applicants respectfully note the following:

1. The experiments carried out by DeFatta and De Benedetti (*Cancer GeneTherapy* 9:502-512 – 2002) and which were included in the Patent Application as examples, were carried out with immunocompetent animals (BalbC mice).
2. Distribution of vector to all tissues by systemic administration was demonstrated by end-point and real-time PCR (Fig.3 of the paper). Efficacy in regression of lung metastases was demonstrated in Fig. 5.
3. Specific expression only in tumors, in the face of general transfection of all tissues, has been demonstrated in the DeFatta article by the lack of systemic toxicity, in contrast to the unregulated BK-TK vector.

While the Examiner contends that the administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection, Applicants respectfully note the following:

1. In the DeFatta and DeBenedetti article referred above, the DNA can also be delivered not only as naked DNA but encapsulated in liposomes. Hence, the DNA is also deliverable in a form protected from nucleases in the plasma and immune cells as well known in the art.
2. Efficient delivery and transfection of all tissues by systemic administration was demonstrated (see above).

3. There have been many advances in the use of even naked DNA for gene transfer in animals. For example, see a review by Heweijer and Wolff. Gene Therapy 10: 453-458 - 2003. "Progress and Prospects: naked DNA gene transfer and therapy." (See attached Declaration of A. DeBenedetti and Heweijer and Wolff review attached herein). The review lists numerous methods, from electroporation into muscle and skin, to tail vein systemic delivery of plasmid DNA and oligonucleotides.

Applicants further respectfully assert that the Office has not provided convincing evidence as to why the results achieved using the art-recognized model disclosed in applicants' specification cannot be correlated to efficacy in non-human primates or humans.

Quantity of Experimentation

The Examiner cites *Kirn et al.* (Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002) to contend that the art recognizes that a high level of experimentation is required for the development of a viable and efficacious GDEPT cancer therapy despite a showing that the present invention is proven viable.

Applicants respectfully disagree. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination.

As set forth above, applicants have provided working examples that show the use of different DNA sequences to control gene expression that constitutively expresses the toxin in all cell types. The determination of the appropriate vector and dosage of plasmid DNA or levels of expression that would be effective in treating tumors and the proper sequence for expressing the toxin in the tumor cells would necessarily be determined empirically and would be considered merely routine in the relevant art. Dosages of therapeutic agent effective in treating tumors are routinely extrapolated by methods known in the art. (See attached Declaration of A. DeBenedetti).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Here, any experimentation, if it in fact is deemed necessary, would be considered well within the ordinary course of the art and would not be considered undue.

An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 8 USPQ2d at 1404 (CCPA 1076). The quantity of experimentation can be "considerable," "tedious," "laborious," and "time-consuming," as long as the experiments are merely "routine." Here, the specification already shows that direct delivery works in immuno-competent animals.

In fact, the specification meets the enablement requirements of § 112 for the full scope of the claims in that the application discloses the intended patients, therapeutically effective amounts of the vector to be administered, exemplary routes of administration, the intended therapeutic product, and the intended disease. The specification does not broadly claim gene therapy techniques without demonstrated, working examples. In fact, the specification provides multiple working examples showing striking results. These examples show that the claimed DNA sequence were successfully delivered and expressed in both the *in vitro* and *in vivo* environment, resulting in a dramatic improvement in disease state.

Conclusion

As such, applicants respectfully submit that, in view of the extensive direction and guidance provided, the presence of working examples for in vitro and in vivo gene therapy, the

relative breadth of the claims, and the evolved state of the art with respect to gene therapy at the time of filing, practice of the claimed invention would not require undue experimentation, and the requirements of § 112, First Paragraph have been met.

In light of the remarks made herein, along with the references and Declaration of A. DeBenedetti attached, it is respectfully submitted that the rejections under 35 U.S.C. §112 have been overcome and should be withdrawn. Accordingly, the present application as amended is now in form for allowance and early reconsideration and allowance of the claims, as currently pending, is earnestly solicited.

Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com if clarification is necessary.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226. Applicants believe that no additional extensions of time or fees are required to complete the filing of this document. However, if such additional extension of time or fee is required the Commissioner is authorized to charge such fees to Applicant's Deposit Account No. 06-2226.

Respectfully submitted,

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